INTERNATIONAL JOURNAL OF RESEARCH CULTURE SOCIETY
Monthly Peer-Reviewed, Refereed, Indexed Journal
Volume - 10, Issue - 6, June - 2026

ISSN(O): 2456-6683
[Impact Factor: 9.241]

IJRCS

DOIs:10.2017/IJRCS/202606011 --:-- Research Paper / Article / Review

Advanced Drug Delivery System For Transungual Therapy: Current Strategies And Future Perspectives

Utkarsh Gupta[1], Neeraj Kumar Prajapati[2], Dr. Anurag Kumar[3]

[1]M. Pharm (Pharmaceutics) Student, Shree Krishna College of Pharmacy, Sitapur, Uttar Pradesh, India, 261125, (Affiliated to Dr. A.P.J. Abdul Kalam Technical University, Lucknow, Uttar Pradesh, India)

[2]Assistant Professor, Department of Pharmaceutics, Shree Krishna College of Pharmacy, Sitapur, Uttar Pradesh, India, 261125

[3]Professor, Department of Pharmacology, Shree Krishna College of Pharmacy, Sitapur, Uttar Pradesh, India, 261125

Email: [1]utkarshrishu2018@gmail.com, [2]Neerajkumarprajapati38@gmail.com, [3]anuknp80@gmail.com

Abstract: *Onychomycosis is a common fungal infection of the nail unit, which is particularly difficult to manage because the dense keratinized structure of the Nail Plate (NP) restricts the penetration of therapeutic agents. Some of the limitations associated with other forms of treatment include systemic toxicity, non-adherence to treatment by the patient as well as inadequate delivery of the drugs to the site of infection. The aim of this narrative review is to provide the general overview of the recent advances in transungual drug delivery systems (TDDS) and to give a particular focus on the strategies which have been developed within the period between 2018-2026. It is a critical analysis of structural and physicochemical obstacles of the nail, traditional treatment hindrances and application of modern delivery modes like microspheres, nanoparticles, vesicular carriers and physical enhancement techniques. Microspheres-in-gel systems have gained considerable attention because they combine sustained drug release with enhanced nail hydration and prolonged residence time, thereby improving drug permeation and retention. The review also identifies important polymers, formulation techniques as well as evaluation techniques used in the research of transungual delivery. Although encouraging in vitro and ex vivo results exist, there still exists a large gap in clinical translation due to a lack of clinical trials and scalability. The future outlook focuses on how smart delivery systems, artificial intelligence, and combination therapies could be used to enhance the therapeutic outcomes.*

Keywords: *Onychomycosis, Transungual drug delivery, Nanoparticles, Microspheres, Nail permeability, Antifungal therapy.*

1. INTRODUCTION

Onychomycosis is a chronic fungal infection of the nail unit that primarily affects the NP, bed, and matrix, which contributes to almost half of all nail conditions in the world. It is a very common cause especially in the elderly population, immunocompromised people and patients with diabetes, thereby contributing to the reduced quality of life as a result of pain, discoloration and nail deformity. Onychomycosis has been on the rise as a global disease burden with the prevalence rates ranging between 5-20% based on geographic and demographic conditions.[1] It is mostly produced by dermatophytes (i.e. Trichophyton mentagrophytes and Trichophyton rubrum) but yeasts as well as non-dermatophyte

ISSN(O): 2456-6683
[Impact Factor: 9.241]

molds (i.e. Candida species) are often involved, especially in immunocompromised patients.[2] The etiology of infection and nail structure is complex makes effective treatment especially difficult.

The existing therapeutic solutions of onychomycosis are systemic also topical antifungal therapy. Oral antifungal agents like terbinafine and itraconazole are commonly prescribed because of their potential to reach the nail bed via systemic circulation, but their use is often associated with important limitations, including hepatotoxicity, drug-drug interactions, prolonged therapy, and emerging antifungal resistance.[3] Conversely, topical therapies including nail lacquers, creams and solutions provide localized therapy with fewer systemic side effects but are poor at drug penetration across the dense keratinized NP resulting in poor therapeutic outcomes.[4] These restriction highlight the necessity for additional effective and targeted drug delivery strategies.

A promising alternative approach has been identified transungual drug delivery which attempts to deliver therapeutic agents directly across the NP to the site of infection though avoiding systemic exposure. In spite of major achievements and innovations in the field of formulation science, namely nanocarriers and other delivery systems, a certain gap remains between the success of the experiments and the clinical implementation.[5] Numerous complex systems have shown better permeation and antifungal activity in vitro, but fail to produce consistent clinical results due to other factors.[6] Thus, it is highly necessary to address this gap through the development of robust, patient compliant and effective transungual delivery systems.

2. NAIL BARRIER AND DRUG PENETRATION

- **Nail Structure**

The human NP is a highly specialized keratinized structure that is the major barrier to the penetration of drugs in transungual delivery. It is mainly composed of hard keratin, which is a fibrous protein with a high concentration of cysteine residues that form large disulfide bonds and contribute to rigidity and mechanical strength of the NP. This keratinized mesh is packed into 3 distinct layers, namely, intermediate, dorsal, and ventral layers which differ slightly in their composition and porosity but form a compact and highly cross-linked structure.[7] In comparison with stratum corneum of the skin, NP has a very low lipid content that considerably restricts the diffusion of lipophilic drugs and changes the permeation profile of therapeutic agents. The tightly packed keratin filaments and narrowing of the intercellular spaces further limit the mobility of the molecules, making NP an extremely difficult barrier to perform topical drug delivery.[8]

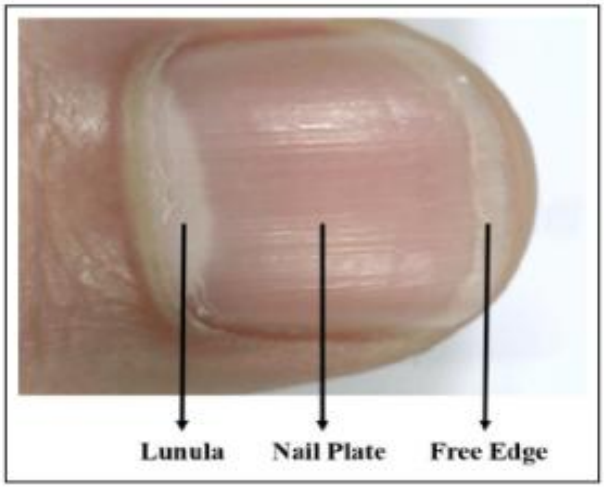

Figure 1 Structure of the NP (Source: Lee *et al.*, 2018)

ISSN(O): 2456-6683
[Impact Factor: 9.241]

- **Drug Transport Pathways**

The passage of drugs across the NP is mainly through two routes such as transcellular and intercellular route. The transcellular pathway entails the transport of drug molecules directly through the keratinized cells and involves diffusion through dense keratin networks. The intercellular pathway is by diffusion along very small (when compared with those in the skin) gaps between the keratinocytes.[9] The physicochemical characteristics of the drug especially its molecular size, hydrophilicity and lipophilicity are very important in determining the predominant mechanism of transport. Hydrophilic drugs tend to permeate through the hydrated keratin matrix better, because the NP will act more like a hydrogel since it is attracted to water. Lipophilic drugs are generally more resistant since the nail has a low lipid content, which leads to low partitioning and slow diffusion rates. Moreover, drug ionization and molecular weight are also highly important factors that affect permeability, where smaller, moderately hydrophilic molecules show relatively better penetration profiles.[10]

- **Challenges in Drug Penetration**

Although the formulation strategies have made progress, there are still some inherent factors that have hindered the delivery of the drugs in the NP. Further, several drugs have a high affinity towards keratin resulting in binding interactions that cause the loss of the amount of free drug that can act as therapy.[11] The slow rate of nail growth, which is usually 2-3 mm per month of fingernails and even slower for toenails, further delays the process of infection clearing and increases the duration of treatment. The other significant problem is that under normal conditions, the NP is limitedly hydrated, which limits the swelling of the keratin and reduces permeability. The loss of drugs on the nail surface due to environmental exposure, repeated washing, and mechanical stress may also lead to diminished treatment efficacy. Collectively, limited nail hydration, strong drug–keratin interactions, and slow nail growth significantly reduce drug permeation and prolong treatment duration, thereby necessitating advanced transungual delivery strategies.[12]

Table 1 Characteristics of the NP's Structure and Barrier

Parameter	Description	Impact on Drug Delivery
Keratin content	Highly cross-linked hard keratin	Restricts diffusion
Disulfide bonds	Strong sulfur linkages	Increases rigidity
Lipid content	Very low	Limits lipophilic drug transport
Hydration level	Low under normal conditions	Reduces permeability
Thickness	0.25–0.6 mm	Barrier to penetration

3. CONVENTIONAL FORMULATIONS

- **Types of Conventional Transungual Formulations**

The treatment of onychomycosis has traditionally connected with usage of the topical dosage such as nail lacquers, solutions as well as creams. Nail lacquers are the most common as it is possible to create a layer on the nail surface and provide a slow release of the active agent. These formulas generally contain antifungal compounds such as amorolfine or ciclopirox within a polymeric base which enhances the adhesion on the NP. Solutions are another popular form, the advantage of which is that it is easy to apply and dry on the nail surface; but they often lack sufficient residence time on the nail surface. Creams and ointments show limited efficacy in transungual delivery due to inadequate penetration across the keratinized nail plate.[13]

- **Limitations of Conventional Formulations**

Conventional topical formulations exhibit limited clinical efficacy because the dense keratinized nail plate restricts drug diffusion to deeper infected regions.[14] In addition, prolonged treatment duration and frequent application reduce patient adherence, particularly in severe onychomycosis involving the nail bed and matrix. Consequently, conventional formulations often fail to achieve sufficient therapeutic concentrations, highlighting the need for advanced transungual delivery systems.[15]

ISSN(O): 2456-6683
[Impact Factor: 9.241]

4. ADVANCED DRUG DELIVERY SYSTEM(DDS)

- **Microspheres**

Microsphere-based DDS have received a portion of interest in the transungual therapy because of their capability to offer controlled and constant release of antifungal agents. These systems are normally made of biodegradable or non-biodegradable polymers that enclose the drug within a matrix or reservoir structure. Considering nail delivery, microspheres can increase the residence time of drugs on the nail surface and a deeper penetration of the drugs into the NP.[16] The type of polymer used, compatibility of drugs with polymers, and the method of preparation are the main factors that influence the performance of microspheres and shall be discussed in the following sections. In spite of these benefits, other challenges like even distribution of particle sizes and scaling are areas of current research.

- **Nanoparticles**

Delivery systems that involve nanoparticles are one of the most promising methods of breaking the very strong obstacle of the NP. Polymeric nanoparticles that are usually prepared using materials like Poly (lactic-co-glycolic acid) (PLGA) or chitosan offer controlled drug delivery and enhanced stability thus making them suitable in sustained antifungal therapy.[17] Lipid-based nanoparticles, such as Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs), are more easily absorbed by the keratinized nail matrix because of their lipophilic properties, and thus improve drug permeation. Also, liquid crystalline nanoparticles have become a new generation of advanced carriers that offer both structural organization and a high drug-loading capacity in addition to enhanced stability.[18]

- **Vesicular Systems**

Transungual methods, including the usage of vesicular drug delivery systems, e.g. liposomes and transfersomes, have also been studied on the basis of their unique structural and functional features. Liposomes are the spheres that are vesicles and composed of bilayers made of phospholipids which can also entrap both the hydrophilic and the lipophilic drugs which gives a freedom in designing the formulations. Their comparative hardness may however obstruct a deep penetration into the thick nail matrix. In contrast, transfersomes are very deformable vesicles capable of squeezing through the narrow intercellular spaces and improve drug delivery across biological barriers. Although these advantages exist, the agglomeration of vesicles, lack of stability, and high costs of production are some of the challenges that make their useful application in transungual therapy difficult.[19]

- **Physical Enhancement Techniques**

Besides the chemical and carrier-based methods, physical enhancement methods have been invented to improve the penetration of drugs across the NP. Iontophoresis is a non-invasive procedure that involves the application of low electrical current that drives the charged drug molecules through the nail.[20] Another new technology that incorporates laser energy to create microchannels or break down nail structure to allow increased drug penetration is laser-assisted drug delivery. It has been clinically established that the combination of laser therapy with topical antifungal therapies may have a significant beneficial effect on the therapeutic outcome. Collectively, these methods demand special equipment, trained personnel and may be costly and thus is not accessible to most regular clinical practice.[21]

- **COMPARATIVE INSIGHT OF ADVANCED SYSTEM**

Table 2 Comparative Insight of Advanced Systems

System	Mechanism	Advantages	Limitations	Key Study
Microspheres	Controlled release via polymer matrix	Sustained drug release, improved retention	Scale-up challenges, variability in size	Prajapati *et al.,* 2025
Polymeric Nanoparticles	Drug encapsulation in polymeric carriers	Enhanced penetration, stability	Complex formulation, cost	de Matos *et al.,* 2025
Lipid Nanoparticles	Lipid-mediated diffusion through keratin	Improved permeation, biocompatibility	Stability issues	Prajapati *et al.,* 2025

ISSN(O): 2456-6683
[Impact Factor: 9.241]

Laser-assisted delivery	Microchannel formation via laser disruption	Deep penetration, improved efficacy	Expensive, requires expertise	Konisky *et al.,* 2024
Liquid Crystalline NPs	Structured nanocarriers with high drug loading	Controlled release, enhanced interaction with nail	Limited clinical data	Leu *et al.,* 2023
Liposomes	Phospholipid vesicle encapsulation	Biocompatibility, dual drug loading	Limited penetration	Witika *et al.,* 2021
Transfersomes	Deformable vesicles enabling deeper penetration	Enhanced permeability	High production cost	Witika *et al.,* 2021
Iontophoresis	Electrical current-driven drug transport	Increased permeation, reduced treatment time	Equipment-dependent	Nair *et al.,* 2021

Although nanoparticle- and vesicle-based systems demonstrate superior permeation enhancement, their formulation complexity, stability concerns, and manufacturing costs remain major translational barriers. In contrast, microsphere-based systems provide sustained drug release and improved formulation stability but may face challenges related to scale-up and reproducibility. Physical enhancement techniques such as iontophoresis and laser-assisted delivery can substantially improve nail penetration; however, their dependence on specialized equipment limits routine clinical applicability. Consequently, future transungual strategies should focus not only on permeation enhancement but also on scalability, patient compliance, and long-term clinical effectiveness.

5. MICROSPHERES-IN-GEL SYSTEM

- **Concept of Hybrid Delivery System**

One highly promising hybrid method in transungual drug delivery, combining the benefits of particulate carriers with semi-solid formulations is the microspheres-in-gel system. In this type of system, the drug-loaded microspheres are dispersed uniformly in a gel matrix to give rise to a dual-functional system, which enhances drug retention and penetration through the NP.[22] Consequently, this approach has received growing interest over the recent years owing to its capacity to address the limitations of traditional topical systems, especially the lack of adhesion and rapid loss of drugs. The gel component provides long-term contact with the surface of the nail, whereas the microspheres embedded into the gel provide long-term contact with the surface of the nail. These hybrid systems are especially beneficial in the treatment of chronic diseases such as onychomycosis, in which effective treatment of the fungus requires prolonged therapy.[23]

- **Mechanism of Drug Delivery**

The microspheres-in-gel systems mechanism is based on the synergistic interaction of the two components. This is achieved by using microspheres that contain the antifungal drug in a polymeric matrix allowing controlled and sustained release over a prolonged period. This aids in a steady drug concentration gradient throughout the NP to allow increased diffusion into deeper layers. At the same time, the gel matrix is important to enhance drug delivery, providing adhesion to the nail surface and enhancing hydration of the keratin structure. The swelling of the NP due to hydration causes the loosening of the tightly packed keratin network and increases the drug permeability. Gels composed of poloxamers, especially, have demonstrated an attractive thermoresponsive behavior, which can easily be applied and retained better at the site of action.[24]

ISSN(O): 2456-6683
[Impact Factor: 9.241]

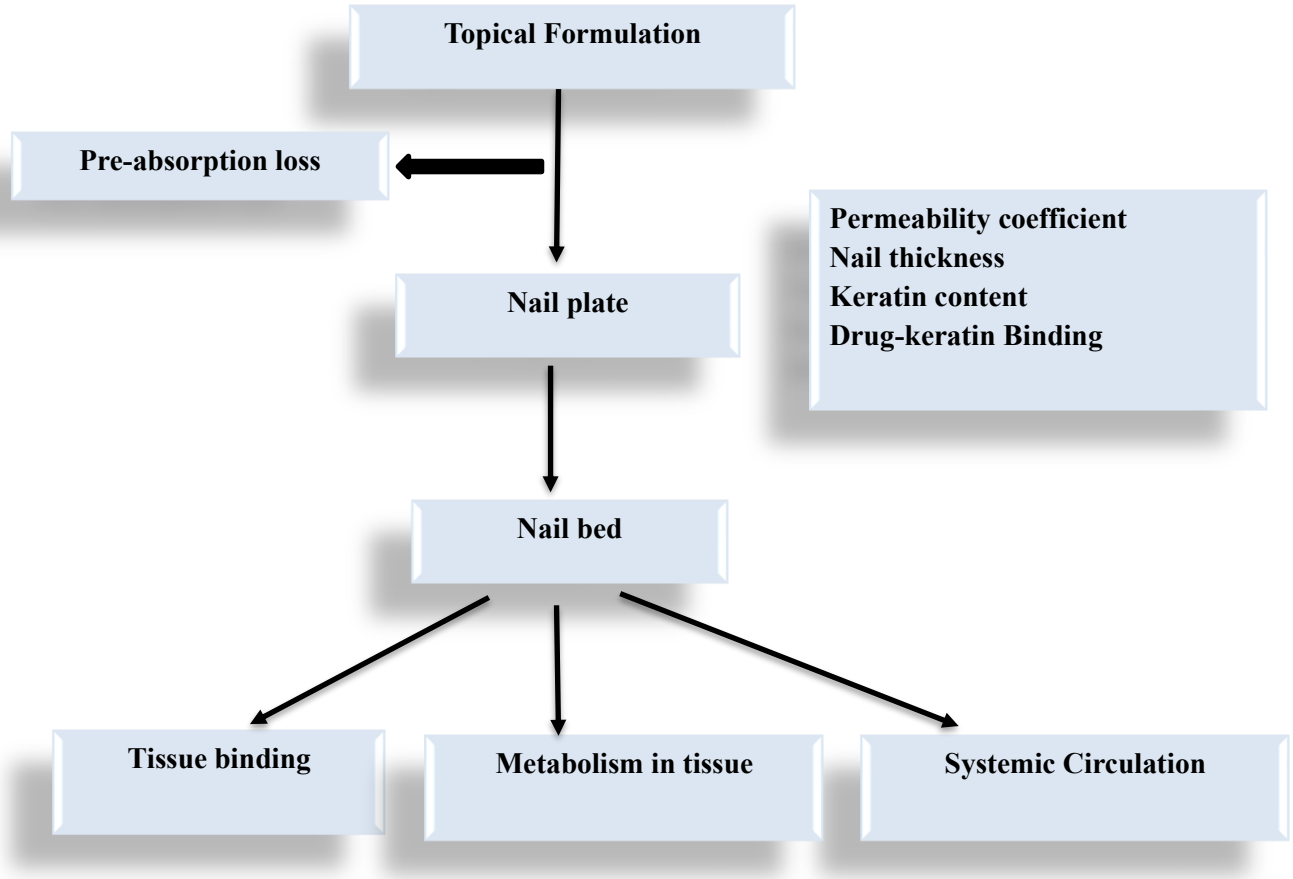

Figure 2 Microspheres-in-Gel Drug Delivery Mechanism (Source: Self-Created)

- **Advantages of Microspheres-in-Gel Systems**

Among the most important benefits of the microspheres-in-gel systems is that the drug residence time on the nail surface is greatly increased. The gel has a hydration effect that increases drug permeation into the nail barrier by altering the physical characteristics of the nail barrier.[25] The release of drugs in microspheres can be controlled to decrease the number of applications and thus enhance patient compliance. These systems lower the systemic exposure and resulting side effects by targeting the drug locally in a specific manner. Recent studies have demonstrated improved antifungal efficacy and nail drug retention using chitosan nanoparticle-loaded poloxamer gels. In spite of these merits, there also exist challenges connected with stability and scalability of the formulations that should be resolved to successfully translate it to clinical.[26]

6. POLYMERS & PREPARATION METHODS

- **Polymers Used in Transungual Delivery**

Polymers are important in determining the design and performance of TDDS, especially in microsphere and gel formulations. Ethyl cellulose has gained popularity because of its hydrophobic property and its capacity to provide a sustained drug release effect by creating a diffusion barrier. Other widely used biodegradable polymer, which can be useful in encapsulation of antifungal agents, includes PLGA.[27] Chitosan is a natural polymer, which is appreciated owing to its bioadhesive nature and capacity to increase drug permeation by reacting with keratin. Poloxamer is a thermoresponsive polymer commonly referred to as Poloxamer and is frequently used in gel formulations because it is capable of passing through several phases, namely liquid, gel, liquid and gel, depending on the temperature at which it is maintained.[28]

ISSN(O): 2456-6683
[Impact Factor: 9.241]

- **Preparation Methods**

The oil-in-water (O/W) emulsion solvent evaporating technique is one of the widely used preparation procedures to prepare microspheres. This is accomplished by combining the drug and the polymer to a solution in an organic solvent and subsequently emulsified in an aqueous phase and then the solvent is evaporated to form solid microspheres.[29] Another commonly used method is spray drying where a polymer-drug solution is atomized in a hot drying chamber, causing the solvent to evaporate quickly and the formation of fine particles. The type of preparation used is dependent on the physicochemical attributes of drug and the characteristics required of the final product.[30]

The efficiency of microsphere preparation is strongly influenced by formulation and process variables including polymer concentration, solvent volatility, emulsifier type, stirring speed, and phase ratio. For instance, increasing polymer concentration generally increases particle size and prolongs drug release, whereas higher stirring speeds produce smaller microspheres with improved surface uniformity. Similarly, solvent selection affects encapsulation efficiency and particle morphology. Optimization of these parameters is essential to achieve reproducible formulations with adequate drug loading, controlled release behavior, and enhanced nail permeation. From a translational perspective, scalable manufacturing techniques and batch-to-batch consistency remain critical challenges for commercial development.

- **Factors Affecting Formulation**

A number of parameters in formulation have a profound effect on the performance of transungual delivery systems. Drug-to-polymer ratio is a key parameter which determines the drug loading efficiency and release profile; higher polymer content typically results in slower drug release.[31] Solvency system used is also a crucial factor in determining the particle size, encapsulation efficiency and stability of the formulation. Moreover, such parameters like the stirring speed, temperature, and the emulsifier concentration can influence the properties of microspheres. Careful optimization of these formulation variables is necessary to achieve reproducible drug release behavior, adequate nail permeation, and long-term formulation stability.[32]

7. EVALUATION TECHNIQUES

- **Drug Release Studies**

A study on the drug release in vitro is needed to assess the performance of TDDS. One of the most popular pieces of equipment used for this purpose is the Franz diffusion cell which can simulate diffusion across a membrane of a drug under controlled conditions. Release kinetics models such as zero-order, first-order, and Higuchi equations are commonly applied to characterize drug release behavior and predict sustained delivery profiles.[33]

- **Nail Permeation Studies**

Nail permeation research is completed to determine the capability of drug formulations to enter the NP and reach the infection site. These analyses are normally conducted by the use of human or animal nail models attached to diffusion cells. More frequently, advanced analytical methods are used to measure drug concentration in the various layers of the nail, giving information on the formulation effectiveness.[34]

- **Antifungal Evaluation**

Microbiological examines such as determination of Minimum Inhibitory Concentration (MIC) of a compound and zone of inhibition studies are most common methods used to determine antifungal efficacy of formulations.[35] MIC assays are used to ascertain the lowest concentration of drug that can inhibit fungal growth and the zone of inhibition studies give a visual representation of the antifungal activity.[36]

- **Characterization Techniques**

The quality as well as performance of transungual formulations must be guaranteed through comprehensive characterization of these formulations. The analysis of the size of the particles is important to nanoparticle and microsphere systems because it determines the drug release and permeation. Scanning Electron Microscopy (SEM) is the method of exploring the surface morphology and structural properties of particles. Drug loading efficiency and

encapsulation efficiency are also measured to find out the quantity of drug that has been loaded successfully into the delivery system. These characterization methods are critical in formulation optimization and quality control, and ultimately effective transungual DDS can be developed.[37]

Although these evaluation methods provide valuable preliminary data, their predictive value for clinical performance remains limited. Variability in nail thickness, hydration status, and keratin composition among patients may significantly influence drug permeation outcomes. Therefore, standardized testing protocols and clinically relevant nail models are necessary to improve the translational reliability of transungual formulations.

8. RESEARCH GAPS & FUTURE SCOPE

- **Current Gaps in Transungual Drug Delivery**

Although there has been tremendous progress in the development of formulation strategies to be used in transungual therapy, there have been several gaps that have been critical in the positive clinical conversion of the formulation strategies. One of the most prominent limitations is the lack of well-designed clinical trials evaluating the efficacy and safety of advanced DDS such as nanoparticles, microspheres, and hybrid gels. Most of the studies that are available are limited to either in vitro or ex vivo models, which, whilst effective in preliminary assessment, do not accurately replicate the complex physiological conditions of the human nail unit. Consequently, clinical evidence supporting the widespread implementation of these systems remains limited.

Another major issue is the absence of actual life data on long term treatment outcomes, patient adherence and incidence rate. Onychomycosis is a chronic disease, with high rates of relapse, and a longitudinal clinical data does not exist to establish the long-term efficacy of new therapies. The uncertainty of the patient-specific variables such as nail thickness, hydration and comorbidities only contributes further to the impossibility of generalizing the experimental findings to similar clinical outcomes.[38]

The major interruption is also scalability and manufacturing feasibility. Many of the high-level formulations are defined in terms of the complicated preparation procedure, special materials and stricter processing conditions that can delay large scale production and overall costs. This presents an obstacle to commercialization and availability, especially in resource-constrained environments. Furthermore, the issues of the formulation stability, reproducibility, and regulatory approval are not dealt with appropriately. It is a combination of these gaps that have indicated the need to have more integrated ways of research that would be useful in bridging the gap in laboratory innovation and practical clinical application.

- **Emerging Trends and Future Perspectives**

The combination of new technologies and the interdisciplinary approach that is determining the future of transungual drug delivery. AI in the diagnosis of nail diseases and optimization of their treatment is one of the most capable aspects.[39] The AI-based image analysis and diagnostic platforms are becoming non-invasive instruments with the potential to precisely identify nail disorders and monitor response to treatment. The technologies can be used to enhance early detection, treatment choices, and customized plans of treatment.[40]

At the same time, development of smart DDS is successful. These systems are designed to respond to some physiological or environmental stimuli, and it enables the desired and controlled release of drugs.[41,42] The applications of the new technologies such as stimuli-responsive polymers, systems based on nanocarrier, and systems based on hybrid formulations are expected to play a vital role in enhancing drug penetration and retention in the nail unit.[43] Furthermore, the use of permeation enhancers and carriers that are based on nanotechnology are also likely to amplify the performance of transungual delivery systems.

The combination therapies are also an attractive prospect in the future research. Such a combination of two or more treatment modalities (e.g. topical formulations in combination with physical enhancement modalities (e.g laser or iontophoresis)) may potentially overcome the limitations of any single treatment modality and may result in the achievement of synergistic treatment effects. In addition, it is possible to combine the antifungal agents with the others, namely, the anti-inflammatory agents or the potent keratolytic ones.

Overall, future research should be focused on effective and efficient clinical trials, scalability of formulations, and application of new technologies to develop patient-centered and effective clinical transungual delivery systems. Such gaps in transferring novel research into practical solutions towards the management of onychomycosis will be critical to fill these gaps during the translation of innovative research into practical solutions.

9. CONCLUSION

The transungual drug delivery has become a very crucial research area focused on overcoming the limitations that come with conventional therapies against onychomycosis. The peculiarities of the NP structure are a great obstacle to the proper drug delivery, therefore, the creation of the new delivery systems is needed. Nanoparticles, vesicular systems and physical enhancement methods have been shown to exhibit better drug permeation and therapeutic potential but their clinical translation has not been as successful due to factors such as stability, scalability and lack of clinical validation.

Among the new systems, microspheres-in-gel systems have proven to have a significant potential due to the ability to combine sustained drug release with enhanced adhesion and hydration which culminate into increased level of drug retention and permeation. Whether such developments have taken place or not, there is an immediate need to carry out well designed clinical research and real-life evaluation to know whether they are effective and safe. Further studies must be in a position to bridge the gap between formulation innovation and clinical application to come up with effective, patient-friendly and commercially viable TDDS.

REFERENCES

1. de Matos SP, de Oliveira Araujo K, Kreutz T, da Veiga Júnior VF, Teixeira HF, Koester LS. Nanocarriers in Ungual Drug Delivery. *Pharmaceutics*. 2025;17(8):1060. doi:10.3390/pharmaceutics17081060
2. Abd-Elsalam WH, Abouelatta SM. Contemporary techniques and potential transungual drug delivery nanosystems for the treatment of onychomycosis. *AAPS PharmSciTech*. 2023;24(6):150. doi:10.1208/s12249-023-02603-x
3. Hussain NV, Premaletha K. Recent advancement in transungual therapies: a comprehensive approach to onychomycosis. *World Journal of Pharmaceutical Research*. 2024;16(4). doi:10.20959/wjpr202416-33517
4. Bedanta B, Nikita D, Dhunusmita B, Arka K, Nasima A. Understanding the drug delivery through nails: a comprehensive review. *Journal of Drug Delivery & Therapeutics*. 2021;11(4). doi:10.22270/jddt.v11i4.4941
5. Thatai P, Khan AB. Management of nail psoriasis by topical drug delivery: a pharmaceutical perspective. *International Journal of Dermatology*. 2020;59(8):915-25. doi:10.1111/ijd.14840
6. Witika BA, Mweetwa LL, Tshiamo KO, Edler K, Matafwali SK, Ntemi PV, Chikukwa MT, Makoni PA. Vesicular drug delivery for the treatment of topical disorders: current and future perspectives. *Journal of Pharmacy and Pharmacology*. 2021;73(11):1427-41. doi:10.1093/jpp/rgab082
7. Lal B, Shukla MK, Srivastava H, Pal PK, Khan W. Contemporary Strategies for Treating Nail Disorders: A Study of Transungual Drug Delivery Systems. *Journal of Pharmaceutical Sciences*. 2025;1(11):940-946. doi:10.5281/zenodo.17628502
8. Sousa F, Ferreira D, Reis S, Costa P. Current insights on antifungal therapy: Novel nanotechnology approaches for drug delivery systems and new drugs from natural sources. *Pharmaceuticals.* 2020;13(9):248. doi:10.3390/ph13090248
9. Fernández-Campos F, Navarro F, Corrales A, Picas J, Pena E, González J, Otero-Espinar FJ. Transungual delivery, anti-inflammatory activity, and in vivo assessment of a cyclodextrin polypseudorotaxanes nail lacquer. *Pharmaceutics.* 2020;12(8):730. doi:10.3390/pharmaceutics12080730
10. Farheen F, Yadav HK, Raizaday A, Dhakad K. Updated perspectives on the diagnosis, Management and novel drug delivery strategies for the treatment of onychomycosis. *Journal of Pharmceutical Negative Results.* 2022;13(8):3669-3690. doi:10.47750/Pnr.2022.13.S08.455
11. Sharma S, Chopra H, Pahwa R, Emran TB, Singh I. Novel transungual drug delivery system for treating onychomycosis. *International Journal of Surgery*. 2023;109(7):2145-7. doi: 10.1097/JS9.0000000000000041
12. Aggarwal R, Targhotra M, Sahoo PK, Chauhan MK. Efinaconazole nail lacquer for the transungual drug delivery: Formulation, optimization, characterization and in vitro evaluation. *Journal of Drug Delivery Science and Technology*. 2020;60:101998. doi:10.1016/j.jddst.2020.101998

13. Lee SH, Yang CS. Fingernail analysis management system using microscopy sensor and blockchain technology. *International Journal of Distributed Sensor Networks.* 2018;14(3):1550147718767044. doi:10.1177/1550147718767044
14. Leu JS, Teoh JJ, Ling AL, Chong J, Loo YS, Mat Azmi ID, Zahid NI, Bose RJ, Madheswaran T. Recent advances in the development of liquid crystalline nanoparticles as drug delivery systems. *Pharmaceutics.* 2023;15(5):1421. doi:10.3390/pharmaceutics15051421
15. Chavan GS, Belgamwar A, Patil KD, Agrawal YO. Mechanistic understanding of onychomycosis progression and current advancement in the transungual drug delivery system. *Critical Reviews in Therapeutic Drug Carrier Systems.* 2025;42. doi:10.1615/CritRevTherDrugCarrierSyst.2024053869
16. Gulhane CA, Motule AS, Atram SC, Mankar LM, Deshmukh DA, Bakal RL. An overview on nail drug delivery system: a promising application for various diseases. *European Journal of Biomedical and Pharmaceutical Sciences*. 2021;8(2):104–110. doi:10.17605/OSF.IO/WHNJR
17. Konisky H, Klinger R, Coe L, Jaller JA, Cohen JL, Kobets K. A focused review on laser-and energy-assisted drug delivery for nail disorders. *Lasers in medical science*. 2024;39(1):39. doi:10.1007/s10103-024-03992-6
18. Kandav G, Verma A. Transungual Drug Delivery: A Holistic Review of Nail Anatomy, Penetration Enhancement Techniques, Formulation Strategies, and Experimental Models. *Journal of Drug Delivery Science and Technology.* 2025:107428. doi:10.1016/j.jddst.2025.107428
19. Kaur S, Kumar M, Bhatia A, Chopra S. A recent review on transungual drug delivery system. *Journal of Dispersion Science and Technology*. 2025;46(10):1510-29. doi:10.1080/01932691.2024.2334012
20. Lee BC, Pangeni R, Na J, Koo KT, Park JW. Preparation and in vivo evaluation of a highly skin-and nail-permeable efinaconazole topical formulation for enhanced treatment of onychomycosis. *Drug Delivery*. 2019;26(1):1167-77. doi:10.1080/10717544.2019.1687612
21. Bhairy S, Momin A, Pednekar M, Madan D, Shaikh A, Bankar R, Pitchika S. A note on the Current status of the trans-ungual delivery of poorly soluble drugs at a glance: formulation perspective. *Asian Journal of Research in Infectious*. 2023;12:1-21. doi:10.9734/AJRID/2023/v12i3244
22. Cutrín-Gómez E, Anguiano-Igea S, Delgado-Charro MB, Gómez-Amoza JL, Otero-Espinar FJ. Effect of penetration enhancers on drug nail permeability from cyclodextrin/poloxamer-soluble polypseudorotaxane-based nail lacquers. *Pharmaceutics*. 2018;10(4):273. doi:10.3390/pharmaceutics10040273
23. Kreutz T, de Matos SP, Koester LS. Recent patents on permeation enhancers for drug delivery through nails. *Recent patents on drug delivery & formulation*. 2019;13(3):203-218. doi:10.2174/1872211313666191030155837
24. Monti D, Mazzantini D, Tampucci S, Vecchione A, Celandroni F, Burgalassi S, Ghelardi E. Ciclopirox and efinaconazole transungual permeation, antifungal activity, and proficiency to induce resistance in Trichophyton rubrum. *Antimicrobial Agents and Chemotherapy.* 2019;63(10):e00442-19. doi:10.1128/aac.00442-19
25. Prajapati SK, Jain A, Bajpai M. Lipid-based nanoformulations in onychomycosis therapy: addressing challenges of current therapies and advancing treatment. *RSC advances.* 2025;15(10):7799-7825. doi: 10.1039/D5RA00387C
26. Davies-Strickleton H, Cook J, Hannam S, Bennett R, Gibbs A, Edwards D, Ridden C, Ridden J, Cook D. Assessment of the nail penetration of antifungal agents, with different physico-chemical properties. *PLoS One.* 2020;15(2):e0229414. doi:10.1371/journal.pone.0229414
27. Hay R. Therapy of skin, hair and nail fungal infections. *Journal of Fungi*. 2018;4(3):99. doi:10.3390/jof4030099
28. Prashanth S, Umasankar K, Venugopal K. A strategic approach on ungual drug delivery system. *Archives of Medicine and Health Sciences*. 2024;12(2):1–7. doi:10.4103/amhs.amhs_383_24
29. Gupta I, Adin SN, Rashid MA, Alhamhoom Y, Aqil M, Mujeeb M. Linalool-incorporated synergistically engineered modified liposomal nanocarriers for enhanced transungual delivery of terbinafine against onychomycosis. *Materials.* 2023;16(12):4424. doi:10.3390/ma16124424
30. Ullah KH, Raza F, Munawar SM, Sohail M, Zafar H, Zafar MI, Ur-Rehman T. Poloxamer 407 based gel formulations for transungual delivery of hydrophobic drugs: Selection and optimization of potential additives. *Polymers*. 2021;13(19):3376. doi:10.3390/polym13193376
31. Šveikauskaitė I, Pockevičius A, Briedis V. Potential of chemical and physical enhancers for transungual delivery of amorolfine hydrochloride. *Materials*. 2019;12(7):1028. doi:10.3390/ma12071028
32. Nair AB, Al-Dhubiab BE, Shah J, Gorain B, Jacob S, Attimarad M, Sreeharsha N, Venugopala KN, Morsy MA. Constant voltage iontophoresis technique to deliver terbinafine via Transungual delivery system: formulation optimization using box-Behnken design and In vitro evaluation. *Pharmaceutics.* 2021;13:1692. doi:10.3390/pharmaceutics13101692

33. Nikhath M, Sanjana S. Formulation and evaluation of nail drug delivery system of anti fungal drug. *Asian Journal of Pharmaceutical Research and Development.* 2022;10(6):44-52. doi:10.22270/ajprd.v10i6.1189
34. Muthukumar M, Arunpandiyan J, Rajeev T, Thaila R, Jayalakshmi B, Senthilraja M. New insights of transungual delivery of phytoconstituents loaded nail lacquer for therapy of nail diseases. *Indo American Journal of pharmaceutical Research*. 2023;13(6):934-943. doi:10.5281/zenodo.8081182.
35. García-Oreja S, Álvaro-Afonso FJ, Navarro-Pérez D, León-Herce D, Tardáguila-García A, Lázaro-Martínez JL. Diode Laser and Red-Laser Photodynamic Therapy Versus Ciclopirox 8% HPCH Nail Lacquer for the Treatment of Onychomycosis: A Randomised Controlled Trial. *Mycoses*. 2025;68(10):e70121. doi:10.1111/myc.70121
36. Gregoriou S, Kyriazopoulou M, Tsiogka A, Rigopoulos D. Novel and investigational treatments for onychomycosis. *Journal of Fungi.* 2022;8(10):1079. doi:10.3390/jof8101079
37. Khattab A, Shalaby S. Optimized ciclopirox-based eudragit RLPO nail lacquer: Effect of endopeptidase enzyme as permeation enhancer on transungual drug delivery and efficiency against onychomycosis. *AAPS PharmSciTech*. 2018;19(3):1048-60. doi:10.1208/s12249-017-0917-8
38. Puri V, Savla R, Chen K, Robinson K, Virani A, Michniak-Kohn B. Antifungal nail lacquer for enhanced transungual delivery of econazole nitrate. *Pharmaceutics*. 2022;14(10):2204. doi:10.3390/pharmaceutics14102204
39. Ullah KH, Rasheed F, Naz I, Ul Haq N, Fatima H, Kanwal N, Ur-Rehman T. Chitosan nanoparticles loaded poloxamer 407 gel for transungual delivery of terbinafine HCl. *Pharmaceutics*. 2022;14(11):2353. doi:10.3390/pharmaceutics14112353
40. Almuqbil RM, Sreeharsha N, Nair AB. Formulation-by-design of efinaconazole spanlastic nanovesicles for transungual delivery using statistical risk management and multivariate analytical techniques. *Pharmaceutics*. 2022;14(7):1419. doi:10.3390/pharmaceutics14071419
41. Vora LK, Gholap AD, Jetha K, Thakur RR, Solanki HK, Chavda VP. Artificial intelligence in pharmaceutical technology and drug delivery design. *Pharmaceutics*. 2023;15(7):1916. doi:10.3390/pharmaceutics15071916
42. Wang S, Di J, Wang D, Dai X, Hua Y, Gao X, Zheng A, Gao J. State-of-the-art review of artificial neural networks to predict, characterize and optimize pharmaceutical formulation. *Pharmaceutics.* 2022;14(1):183. doi:10.3390/pharmaceutics14010183
43. Hornick T, Mao C, Koynov A, Yawman P, Thool P, Salish K, Giles M, Nagapudi K, Zhang S. In silico formulation optimization and particle engineering of pharmaceutical products using a generative artificial intelligence structure synthesis method. *Nature Communications*. 2024;15(1):9622. doi:10.1038/s41467-024-54011-9